REMARKS

In connection with the Request for Continued Examination (RCE), Applicants respectfully request entry of the foregoing and reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, and in light of the remarks which follow.

Claims 1, 16, 19-27, 29-34 and 40-41 are pending in the application, Claim 2 having been cancelled above without prejudice to or disclaimer of the subject matter therein.

By the above amendments, Applicants amended Claim 1 to further recite that the modified adenoviral fiber has an affinity for the at least one glycosaminoglycan and/or sialic acid-containing cellular receptor of at least about one order of magnitude less than a wild-type adenoviral fiber. Support for this amendment can be generally found in the specification. Applicants also canceled Claim 2 without prejudice or disclaimer. A claim that has been amended in a manner that does not narrow the claim's scope should be accorded its full range of equivalents.

Applicants thank the Examiner for the courtesies extended to their representative during the interview on March 31, 2008. In particular, Applicants thank the Examiner for agreeing that the subject matter of Claim 2 should be examined together with Claim 1 and, thus agreeing to permit Applicants to amend Claim 1 to include the features of Claim 2. Applicants also thank the Examiner for agreeing to favorably consider Applicants' remarks concerning the patentability of the pending claims. Finally, Applicants thank the Examiner for withdrawing the rejection of Claims 1, 16, 19-27, 30-34, 40 and 41 under 35 U.S.C. § 102(e) as being anticipated by Wickham (U.S. Patent No. 6,455,314) and under § 103(a) as being

unpatentable over Wickham in view of Seth (U.S. Patent No. 5,928,944). In view of the foregoing amendments and following remarks, Applicants respectfully submit that all pending claims in the application are in condition for allowance.

Turning now to the Official Action, Claims 1, 16, 19-27, 29-34, 40 and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wickham in view of Wallach (WO 97/37016) and Seth. For at least the reasons that follow, withdrawal of the rejection is in order.

Independent Claim 1, as amended above, defines a modified adenoviral fiber containing at least one mutation affecting one or more amino acid residue(s) of said adenoviral fiber interacting with at least one glycosaminoglycan and/or sialic acid-containing cellular receptor, wherein said amino acid residue(s) are selected from the group of residues consisting of the lysine in position 506, the histidine in position 508, and the serine in position 555 of the wild type Ad5 fiber protein as shown in SEQ ID NO.: 1, or an equivalent position in a non Ad5 fiber protein,
and wherein the mutation comprises:

- the substitution of the lysine in position 506 by glutamine,
- the substitution of the histidine in position 508 by lysine, or
- the substitution of the serine in position 555 by lysine,

or any combination thereof, and wherein the modified adenoviral fiber has an affinity for the at least one glycosaminoglycan and/or sialic acid-containing cellular receptor of at least about one order of magnitude less than a wild-type adenoviral fiber.
(Emphasis added.)

Wickham relates to an alternately targeted adenovirus and includes methods for producing and purifying such viruses as well as protein modifications mediating alternate targeting. (See, Wickham at col. 1, lines 10-15.)

Wallach relates to DNA sequences encoding proteins capable of binding to TRAF2, the proteins encoded thereby, and the use of said proteins and DNA sequences in the treatment or prevention of a pathological condition associated with NF-κB induction or with any other activity mediated by TRAF2 or by other molecules to which said proteins bind. (See, Wallach at page 1, lines 5-10.)

Seth relates to transfection of eukaryotic cells with nucleic acids mediated by an adenovirus, and the augmentation of such transfection through preincubation of nucleic acids with cationic agents. (See, Seth at col. 1, lines 5-10.)

In order establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claimed features. (See, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).) In addition, "all words in a claim must be considered in judging the patentability of that claim against the prior art." (See, *In re Wilson*, 424 F.2d 1382, 1385; 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).) (See also M.P.E.P § 2143.03.)

In addition, in establishing a *prima facie* case of obviousness under § 103, it is incumbent upon the Patent Office to provide reasons *why* one of ordinary skill in the art would have been led to modify the prior art or combine reference teachings to arrive at the claimed subject matter. The requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art, not from Applicants' disclosure. (See, *Ex parte Nesbit*, 25 U.S.P.Q.2d, 1817, 1819 (B.P.A.I. 1992); and *In re Oetiker,*

24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992).) The mere fact that the prior art can be modified does not make such a modification obvious unless the prior art or some other evidence suggests the desirability of the modification. (See, *In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).)

Here, no such factors or motivation for combining Wickham, Wallach and Seth exist. In particular, it appears to Applicants that one of ordinary skill in the art would not have been led to modify the adenoviral fiber proteins of Wickham to include the specific substitutions (i.e., lysine in position 506 with glutamine, histidine in position 508 with lysine, or serine in position 555 with lysine), defined in independent Claim 1, based on the disclosures of Wallach or Seth. In fact, it appears to Applicants that Wickham actually teaches persons of ordinary skill to avoid making substitutions at positions 506, 508 and 555.

For example, Wickham describes adenoviral fiber mutants impaired in binding to the primary CAR receptor. A series of fiber mutants were constructed, three of which encompass modifications in positions 506, 508 and 555 (the Δ K (506) having the Lys residue in position 506 deleted, the H(506)A mutant having the substitution of the His residue in position 506 (which should be 508) by an Ala residue, and the S(551) N+S (555) N mutant with substitutions of the Ser residues in position 551 and 555 by Asm residues, respectively. (See, Wickham at Table 1, col. 18.) However, when tested for CAR binding, none of the fiber mutants demonstrated reduced affinity for that receptor. Thus, these fiber mutants are not listed in Table 2.

Wallach relates to TRAF binding proteins and, more specifically, analogs of TRAF binding proteins that exhibit "conservative" changes, which are not expected to change the size, charge, configuration or biological activity of the protein. (See,

Wallach at page 22, lines 3-6.) In this regard, Wallach provides two lists of possible conservative substitutions. (See, Wallach at Tables 1A and 1B.)

Seth describes an adenovirus-mediated method of plasmid transfection through a co-internalization process. Gene expression is significantly increased when plasmid transfection is performed in the presence of adenovirus or empty capsids (see, Seth at Example 10, col. 25 to 26), especially when bound to the cellular receptor. (See, Seth at Example 5, col. 19.)

Thus, Wickham discloses that modifying adenoviral fibers in the distal part of the fiber protein at positions downstream of residue 492 has no effect on receptor binding. (See, Table 2 of Wickham where mutations reducing CAR binding are located in positions 408-409, 412-417, 420, 474-477 and 487 and 492.) Accordingly, Wickham would lead one of ordinary skill to expect that residues in positions 506, 508 and 555 are not available for interaction with the cellular receptors. Thus, Wickham would not motivate one of ordinary skill to introduce amino acid substitutions at these positions when attempting to impair binding of the fiber to cellular HGS receptors. Indeed, Wickham actually teaches away from making the asserted combination to arrive at the claimed invention.

Wallach does not overcome the deficiencies of Wickham. In particular, Wallach discloses protein analogs that can be generated by introducing conservative substitutions. However, it is important to note the fact that the described conservative substitutions are intended to preserve biological activity of protein analogs (i.e., maintain biological and structural properties of the polypeptide after amino acid substitutions). (See, Wallach at page 22, lines 3-6 and page 24, lines 26-28.) In stark contrast, the amino acid substitutions defined in Claim 1 modify the

fiber protein's biological activity (e.g., its ability to bind with cellular HGS receptors). Therefore, one of ordinary skill seeking to impair adenoviral fiber interaction with cellular receptors would not have looked to the conservative substitutions of Wallach because Wallach states that the conservative substitutions are intended to preserve (not change) the protein's biological activity (e.g., impairment of receptor binding).

Seth also fails to overcome the deficiencies of Wickham. Indeed, Seth fails to disclose or fairly suggest how adenovirus fibers interact with cellular receptors, which amino acid residues are involved in the interaction, or how one should, or even could, modify adenovirus fiber proteins to impair receptor binding.

In view of the varying teachings of the cited references and the failure of the references (or any other evidence) to provide any suggestion whatsoever that one should, or even could, combine specific features of the references to obtain the claimed modified adenoviral fiber, Applicants submit that the Official Action has not demonstrated that one of ordinary skill in the art would have combined the cited references. Thus, Applicants contend that there is no basis, absent the impermissible use of hindsight based on Applicants' disclosure, for combining the references, as suggested in the Official Action. The only motivation for making the claimed modifications comes from the present specification, which teaches the desirability of the claimed combination of features to obtain reduced affinity for glycosaminoglycan and/or sialic acid-containing cellular receptors. However, it is well-established that the motivation for combining references "cannot come from Applicants' invention itself." (See, *In re Oetiker*, 977 F.2d 1443, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992).) That is, the motivation cannot be a product of hindsight reconstruction based on Applicants' own disclosure.

Accordingly, the Official Action appears to have made a hindsight reconstruction. The Official Action asserts that the claimed subject matter would have been obvious based on a hindsight selection of claimed features. Such a combination is improper because the references, viewed by themselves and not in retrospect, do not suggest the combination asserted by the Official Action. (See, *In re Schaffer*, 229 F.2d 476, 108 U.S.P.Q. 236 (C.C.P.A. 1956); and *In re Stoll*, 523 F.2d 1392, 187 U.S.P.Q. 481 (C.C.P.A. 1975).) Here, neither the references nor any extrinsic evidence provide any motivation for combining different features of the references to obtain the presently claimed adenoviral fibers. The only motivation for ignoring the varying teachings of the references is derived from the disclosure of the present application, which is clearly improper.

Applicants also ask that the Examiner consider the fact that the claimed substitutions reduce the claimed adenoviral fiber's affinity for the at least one glycosaminoglycan and/or sialic acid-containing cellular receptor by at least about one order of magnitude less than a wild-type adenoviral fiber. Applicants submit that these results are surprising especially in view of the negative results obtained in Wickham for fiber mutants with modifications at the same positions when tested for CAR binding.

The Federal Circuit has established that evidence arising out of the so-called secondary considerations must always, when present, be considered en route to a determination of obviousness. Indeed, evidence of secondary considerations can be the most probative and cogent evidence in the record. It can establish that an invention appearing to have been obvious in light of the prior art was not. (See, *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983); and *Joy*

Technologies v. Manbeck, 14 U.S.P.Q.2d 1257 (D.D.C. 1990).) In this case, there is clearly no appreciation in any of the cited references, alone or in combination, of the significantly reduced affinity for glycosaminoglycan and/or sialic acid-containing cellular receptors, obtained by the claimed combination of features. In particular, the cited references, even in combination, fail to disclose or suggest that one could make the specific substitutions claimed to arrive at an adenoviral fiber exhibiting affinity for such cellular receptors of at least about one order of magnitude less than a wild-type adenoviral fiber.

Accordingly, even if the Official Action had established a *prima facie* showing of obviousness, which Applicants submit that it has not, the unexpected results achieved by the claimed combination of features would rebut such a showing.

For at least these reasons, Claim 1 is patentable over the combination of Wickham, Wallach and Seth. The remaining claims depend, directly or indirectly, from Claim 1, and are, therefore, also patentable for at least the reasons that Claim 1 is patentable. Reconsideration and withdrawal of the § 103 rejection of Claims 1, 16, 19-27, 29-34, 40 and 41 are respectfully requested.

From the foregoing, Applicants earnestly solicit further and favorable action in the form of a Notice of Allowance.

If there are any questions concerning this paper or the application in general, Applicants invite the Examiner to telephone the undersigned at the Examiner's earliest convenience.

Respectfully submitted,

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